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Nutrition epidemiology of flavan-3-ols: The known unknowns

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ABSTRACT

Nutritional epidemiology has an important role, as it can provide long-term data from large populations and does not rely on surrogate markers for morbidity/mortality. Meaningful interpretation and applications of outcomes from epidemiological studies depend on the accurate assessment of dietary intake, which is currently mainly based on a combination of self-reporting and food composition data.

Flavan-3-ols are a group of bioactives (non-essential dietary components with significant impact on health) that is a possible candidate for the development of dietary recommendations. The breadth of data available on their effect on health also provides the basis for investigating the suitability of the methods currently used in nutritional epidemiology to assess the health effects of bioactives. The outcomes of this assessment demonstrate that the limitations of currently used methods make it virtually impossible to estimate intake accurately from self-reported dietary data. This is due to the limitations of self-reporting, especially from food-frequency questionnaires, and the inability of currently used methods to deal with the high variability of food composition. Indeed, the estimated intake of flavan-3-ols, can only be interpreted as a marker of specific dietary patterns, but not as the actual intake amount.

The interpretation of results from such studies are fraught with serious limitations, especially for establishing associations between intake and health and the development of dietary recommendations. Alternative assessment not affected by these limitations, such as biomarkers, are required to overcome these limitations. The development of nutritional biomarkers is therefore crucial to investigate the health effect of bioactives.

1. Background and introduction

Lifestyle choices, such as smoking, physical activity and diet, are important risk factors for CVD (Danaei et al., 2009; Ezzati and Riboli, 2013) and therefore an important target for disease prevention and health maintenance. In particular a low intake of plant-based foods has been identified as key contributor to disease burden (Lim et al., 2012), and this is reflected in dietary recommendations and guidelines. Apart from those nutrients essential to human life and procreation, plant-based foods contain phytochemicals, so called bioactives, that while not essential to human life, are proposed to affect human health by playing an important role in health maintenance and disease risk reduction. Consequently, there is an increasing interest in developing dietary recommendations and reference values (DRIs) for dietary bioactives (Lupton et al., 2014). Key challenges in this context lie in establishing a common assessment framework for bioactives, such as it exists for essential nutrients, including ways of establishing causality between the dietary intake of a given bioactive and population-based measures of disease risk reduction or health maintenance (Yetley et al., 2017; Food and Nutrition Board, The National Academies of Sciences, Engineering and Medicine, 2017).

1.1. Flavan-3-ols

Flavan-3-ols are a complex group of bioactives, consisting of monomeric and polymeric compounds (Fig. 1). They have been extensively investigated for their role in human health and nutrition. Although the number of studies in this area is considerable, most data currently available derive from small-to medium-scale, short-term (weeks to several months) dietary intervention studies. Such studies inevitably rely on the assessment of surrogate endpoints, such as measures of vascular function (Heiss et al., 2010b), which inherently limits efforts aimed at translating study outcomes into high-rigor impact assessments of disease risk reduction and primary disease prevention (Weintraub et al., 2015; Bikdeli et al., 2017). While available data are promising, there currently exists a paucity of information from large-scale, long-term, randomised trials with mortality or morbidity outcomes. As a consequence, data

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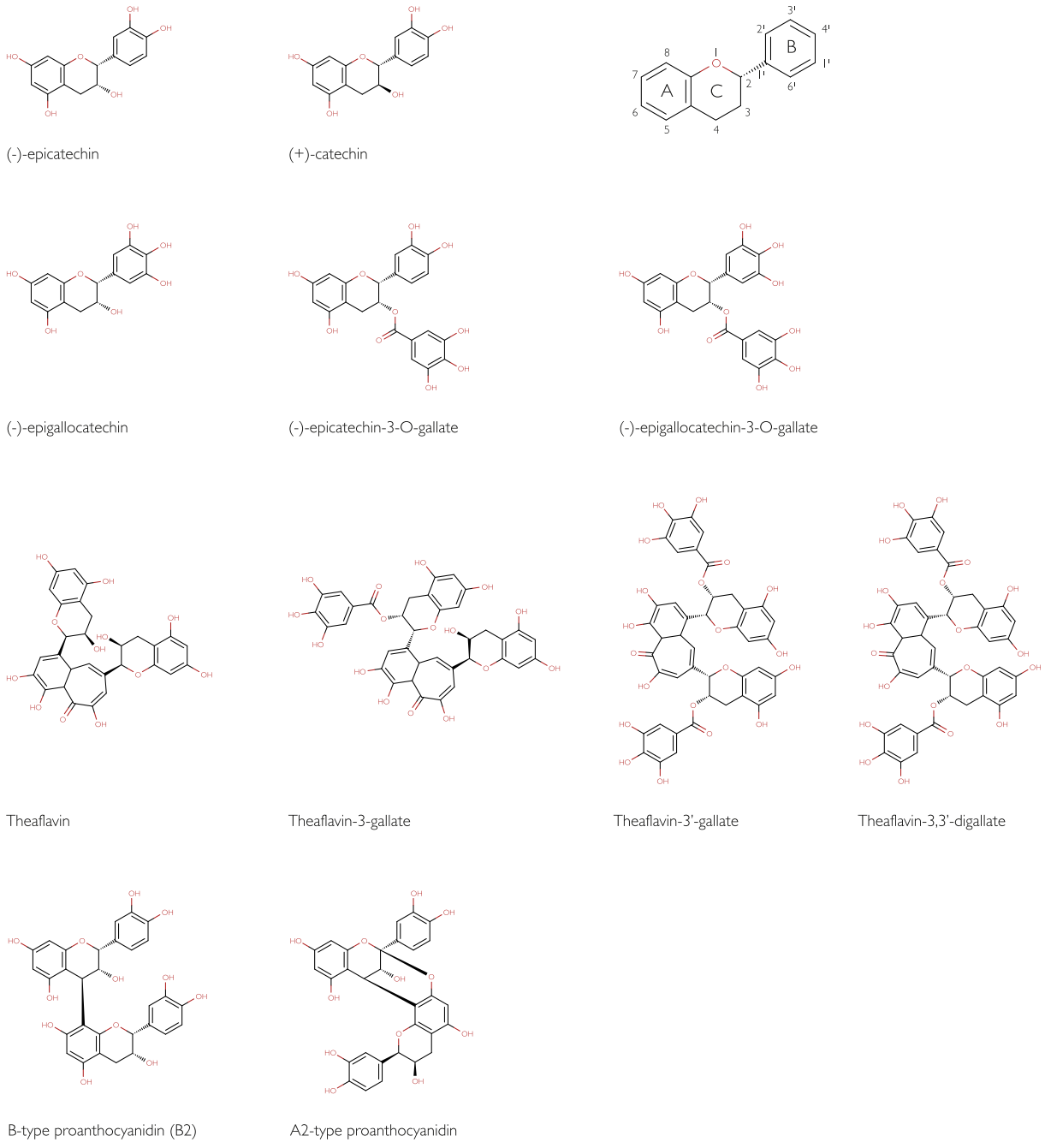

Fig. 1. Structures of monomeric and polymeric flavan-3-ols.

from prospective epidemiological studies may provide information on associations between long-term flavan-3-ol intake and health endpoints, despite of the well-known limitations regarding the establishment of causality (Mayne et al., 2012; Yetley et al., 2017).

This review will focus on currently available data and evaluate the strengths and limitations of nutritional epidemiology in investigating potential associations between flavan-3-ol intake and cardiovascular diseases risk.

2. Prospective epidemiological studies of flavan-3-ols and health

A key advantage of prospective cohort studies is that they can provide long-term data for a large and diverse study population and the opportunity to investigate temporal associations. They also allow to investigate associations with disease risk, and do not require the use of surrogate endpoints, thus providing a better understanding of the association between intake and actual risk. However, epidemiological studies also have several limitations, in particular the vulnerability to confounding factors and difficulties associated with accurate intake assessments. The latter is especially crucial for the validity and applicability of outcome assessments based on data derived from prospective epidemiological studies (Yetley et al., 2017).

In most studies, flavan-3-ol intake is assessed by combining self-reported dietary information with data from food composition databases. While this has been tacitly accepted as *de facto* standard, it introduces a number of limitations that can affect outcomes and

interpretations.

2.1. Assessment of dietary intake

2.1.1. Dietary sources

Flavan-3-ols are one of the most commonly consumed type of flavonoids (Otaki et al., 2009; Bai et al., 2014; Vogiatzoglou et al., 2015b) and they are found in a wide range of different foods. There are large regional differences between dietary sources. In countries with a tea culture such as Japan, Australia or the UK, tea is the main source of total flavan-3-ol intake (Otaki et al., 2009; Somerset and Johannot, 2008; Vogiatzoglou et al., 2015b), whereas in other countries, the main sources are fruits, in particular pome fruits (Vogiatzoglou et al., 2014). These differences also result in a large variation of the type of flavan-3-ol consumed. In countries with high tea intake, these are in particular gallated flavan-3-ols, as well as theaflavins and thearubigins. Conversely, in countries where the main sources are fruits and vegetables, the main types of flavan-3-ols consumed are proanthocyanidins and non-gallanted monomers such as (−)-epicatechin. For example in the UK, where tea is the main source of flavan-3-ols, theaflavins and thearubigins contribute more than half of total flavan-3-ol intake, whereas in Spain, where the main sources are fruits, the main contributor to intake are proanthocyanidins whereas the intake of theaflavins and thearubigins is negligible (Zamora-Ros et al., 2013; Vogiatzoglou et al., 2014).

2.1.2. Self-reported dietary intake

The ideal dietary assessment method should be unbiased and only introduce random error (Carroll et al., 2006; Keogh et al., 2013), but such a method does not currently exist. Most studies rely on self-reported information to estimate diet, and there are a number of well-known limitations: they are prone to recall and person-specific bias (Kipnis et al., 2001), can be affected by social desirability (Hebert et al., 1995, 1997), and often results in specific under- and over-reporting of foods (Freedman et al., 2014). This affects especially those foods perceived to be healthy or unhealthy (Bingham, 1997). These limitations and their impact on research have been discussed extensively (Prentice et al., 2011; Subar et al., 2015). Although methods have been developed to address these shortcomings (Freedman et al., 2015), they have only been applied to a small number of compounds and it is unknown whether they are suitable for bioactives such as flavan-3-ols. The dietary data used in most studies is therefore based exclusively on self-reporting, even though these methods have originally been developed to assess dietary patterns and estimate the intake of nutrients.

Semi-quantitative food-frequency questionnaires (FFQ) are the most commonly used method, especially because they are relatively easy to administer and inexpensive to process (Willett, 2013). They use a limited selection of foods relevant to the target population for which they were developed, and they require calibration studies to estimate nutrient intake accurately (Carroll et al., 1997). This introduces some constraints when applied to food substances, such as bioactives, for which they were not originally designed:

1. Validation data show that FFQ-estimated intakes of individual compounds such as micronutrients often correlate only modestly with true intake (Jacques et al., 1993; Willett, 2013). Data for isoflavones, the only flavonoid group for which there are detailed data, also show only weak correlations between FFQ-estimated and true intake (Yamamoto et al., 2001; Heald et al., 2006); notably this can be improved with FFQs developed to assess isoflavone intake (Frankenfeld et al., 2003; Tseng et al., 2008). However, most FFQs currently used have neither been designed specifically to assess flavan-3-ol intake nor have they been validated. It is therefore unknown how reliable the estimates are that are derived via this approach.
2. Food items listed on FFQs are often grouped based on the dietary habits of the target population and the original research question in the context of which they were initially developed. This often results in the combination of foods with wide ranges of flavan-3-ol content. For example, the EPIC Norfolk FFQ (Mulligan et al., 2014) does not distinguish between red and white wine, even though they differ considerably in both, flavan-3-ol content (47 mg/100 mL vs 2 mg/100 mL) and composition (76% oligomeric proanthocyanidins in red wine vs insignificant amounts in white wine). Similarly, the 2007 Harvard FFQ does not distinguish between apples (24 mg/100 g) and pears (4 mg/100 g), and more importantly, between green and black tea, which differ considerably in flavan-3-ol content and composition (monomeric compounds: 47 mg/100 mL vs 66 mg/100 mL; oligomeric compounds: 24 mg/100 mL vs 5 mg/100 mL; Phenol-Explorer data (Rothwell et al., 2013),). While it is possible to estimate population intake using weighed averages, this is not possible for individual participants of a study and this approach is likely to result in considerable over- or under-estimation of impact and introduces bias (Fig. 2).

Open-ended dietary assessment methods, such as diet diaries (DD) or 24 h dietary recalls (24HDR), are not subject to the same limitations as FFQs, but have not been used in many studies so far (Table 1). However, they are still prone to similar biases, and more importantly, like FFQs they have to rely on food composition data to estimate flavan-3-ol intake.

2.1.3. Food composition databases

As mentioned above, the actual intake of flavan-3-ols, or any other food substance, is estimated by combing data on food consumption with food composition data. For flavonoids, detailed databases have been compiled by the US Department of Agriculture (USDA) (Bhagwat et al., 2004, 2014, 2015) and the Phenol Explorer (Rothwell et al., 2013). The main limitation of this approach is the large variability of food content, which is affected by numerous factors such as variety, growth and harvest condition, storage, food processing and others (Zamora-Ros et al., 2014). Indeed, it is likely that food content varies even in fruits from the self-same plant (Wilkinson and Perring, 1961). In black teas consumed in the UK, flavan-3-ol content varied more than 8-fold depending on variety (Khokhar and Magnusdottir, 2002), and even larger variations were found for green teas (Lin et al., 1998). Such large variability is also found for other foods, for example apples (Sanoner et al., 1999; Rothwell et al., 2013), and other potentially bioactive polyphenols, such as isoflavones (Kuhnle et al., 2009) or anthocyanidins (Gao and Mazza, 1994) (Table 1).

This means that it is virtually impossible to estimate reliably actual intake with methods relying on food composition data. Yet the intake of flavan-3-ols and many other flavonoids is commonly calculated using a single food content value, often based on small-scale of food analyses. Moreover, there is a paucity of validated analytical methods and many data were obtained before the introduction of the AOAC methods (Machonis et al., 2014a, b). The estimated intakes provided by previous studies should therefore be regarded with great caution, and should perhaps best be interpreted as surrogate markers for specific dietary patterns, rather than as accurate intake amounts for flavan-3-ols. Methods developed to address measurement error from self-reporting, such as regression calibration (Freedman et al., 2011), rely on a known and consistent relationship between self-reported and actual intake. However, it is not possible to estimate actual flavan-3-ol content in

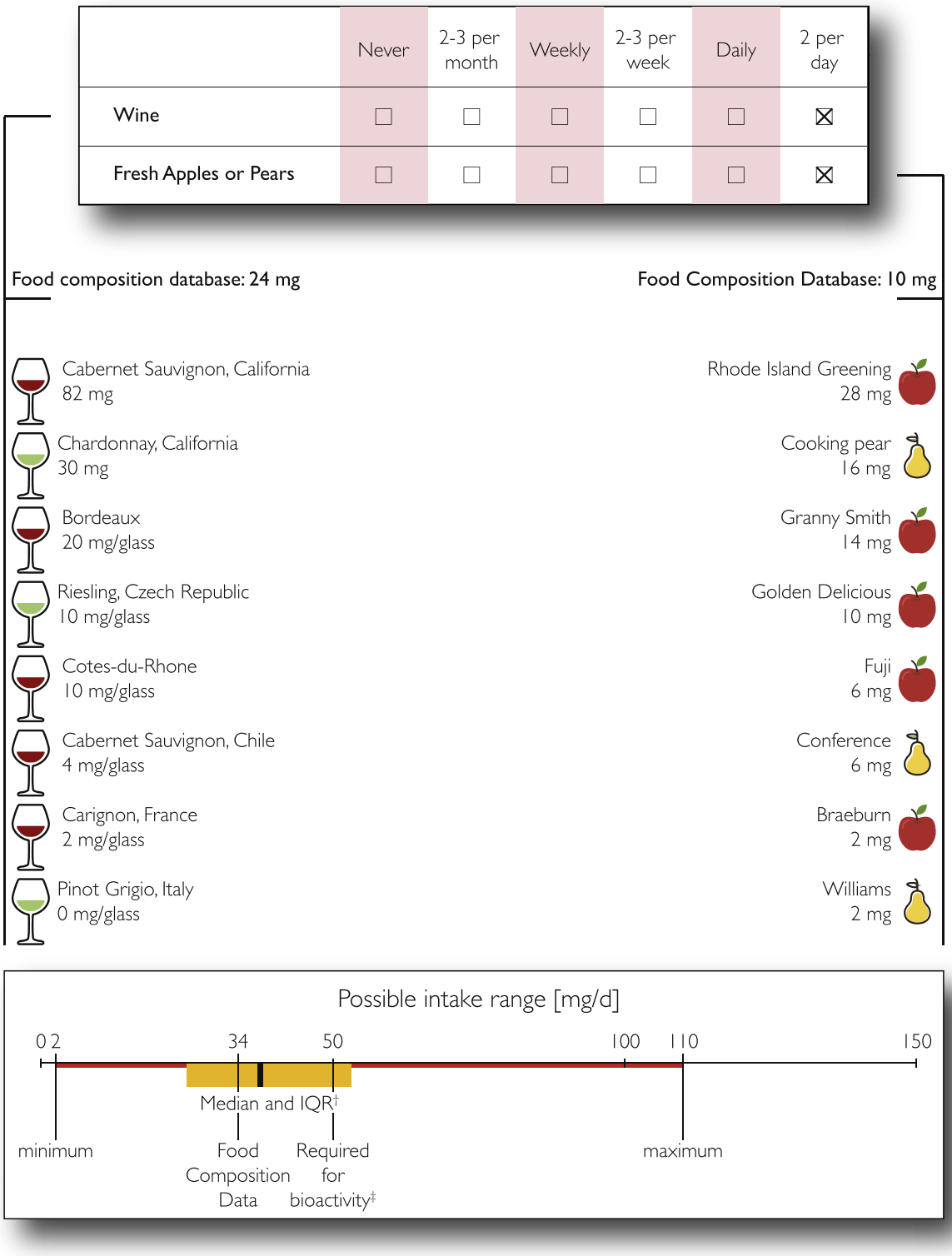

Fig. 2. Bias introduced by the low resolution of food items in FFQs. Estimated (−)-epicatechin intake based on self-reported consumption of two portions of wine, or two portions of *apples and pears*. Data based on Phenol-Explorer and references therein. Data based on simulation of 100,000 participants choosing random combination of wine (two 250 mL glasses of same wine) and two items of the Apple and Pear group. † Inter-quartile range; ‡ based on the assumptions by Hooper et al. (2012) Clipart from Flaticon.

foods from dietary data and therefore such methods cannot be used to improve intake assessment.

In the absence of information on true intake, for example from duplicate diet studies, the difference between true and estimated intake is unknown. However, it is possible to assess the likely impact of the difference using simulations. For the flavan-3-ol (−)-epicatechin, there exist detailed data regarding the range and variability in the flavan-3-ol content of foods commonly consumed

Table 1
Variability of flavonoid content (by subclass) in foods commonly consumed (mean and range in mg/100 g). Data based on Rothwell et al. (2013) and Kuhnle et al. (2009) (isoflavones).

Food	Compound Class	Mean content	Range
Blueberry (Highbush)	Anthocyanidins	134	66–209
Strawberry	Anthocyanidins	73	26–126
Wine (Red)	Anthocyanidins	22	2–77
Onion (Red)	Flavonols	128	58–394
Apple (Dessert)	Flavan-3-ols	24	3–61
Black tea	Flavan-3-ols	73	7–334
Green tea	Flavan-3-ols	71	6–544
Chocolate (dark)	Flavan-3-ols	153	77–273
Apple (Dessert)	Isoflavones	8	5–10
Peas (frozen)	Isoflavones	8	4–11
Savoy cabbage	Isoflavones	3	1–6

in the UK. Fig. 3 shows the comparison of quintiles of (−)-epicatechin intake estimated using two approaches: a) by using the mean value of (−)-epicatechin food content applied to all participants (as is current practice), and b) by using for each participant a random value within the reported range of the (−)-epicatechin food content (see caption for details). Simulating the two approaches based on 25,000 people on a typical UK diet demonstrates that there is only little agreement between the methods (Fig. 3). The high variability in food content therefore does not only affect the estimate of absolute intake, but also the ranking of intake and subsequent assignment in quintiles. As quintiles are often used in nutritional epidemiology to investigate associations between intake and health endpoints, this is likely to have a considerable impact on results.

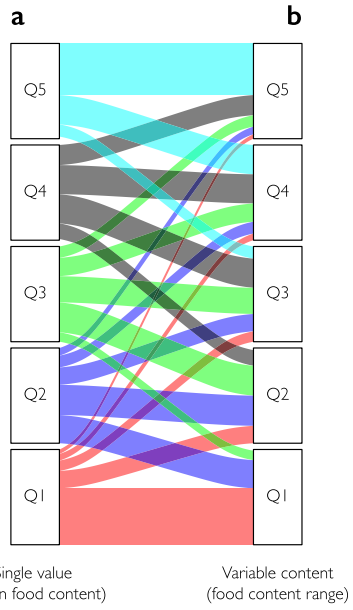

Fig. 3. Impact of food content variability on the classification of participants into quintiles of intake. Comparison of two approaches to estimate (−)-epicatechin intake: a) using the mean food content for all participants as is current practice and, b) by using a random value within the reported range of food content for each participant. Figure is based on the simulation of 25,000 individuals consuming a typical UK diet (National Diet and Nutrition Survey). Food content data are based on mean and range information of the Phenol Explorer database (Rothwell et al., 2013). For approach b), food content for each participant was determined using a normally distributed random number within the given range.

2.2. Interpretation of results

The associations between flavan-3-ol intake and cardio-vascular disease risk and risk markers have been investigated in numerous epidemiological studies (Table 2), which found no or only modest associations. However, all studies relied on self-reporting and food composition database, and it is therefore questionable whether or not the associations found can tenably be attributed to true differences in flavan-3-ol consumption. Indeed, it is likely that the differences observed can only be attributed to specific dietary patterns, for which estimated flavan-3-ol intake is a surrogate marker, but which so far have not been identified. In some instances, estimated intake of flavonoids is likely to be a surrogate marker of social class, for example berries and tea (Song and Chun, 2008; Devore et al., 2012), which could help explain observed beneficial effects (Marmot, 2005).

2.3. Randomised controlled trials (RCT)

The advantage of dietary intervention studies over epidemiological studies is usually the ability to define and characterise the nature of the intervention. However, this is not always the case, and for many studies only limited or no information on the actual composition of the test products or test materials used in a given dietary intervention were available. Whereas for some studies in the context of polyphenol-related dietary interventions the test products were well characterised using validated analytical methods, others used the unspecific Folin-Ciocalteu assay (Folin et al., 1915) and assumed that the only polyphenols present were flavan-3-ols, when in fact such assumptions cannot tenably be made. Indeed, a recent analysis of intervention studies investigating the effect of flavan-3-ols derived from cocoa on cardiovascular disease risk found several studies, where the intervention was insufficiently characterised (Vlachojannis et al., 2016), and Table 3 shows that many studies included in a recent Cochrane review on the effects of cocoa intake on blood pressure (Ried et al., 2017) provide only limited information about the intervention used.

2.3.1. Intake-response relationship

There are large differences regarding the amount of details provided about the type of dietary intervention used in RCTs. Differences in the interpretation of flavan-3-ol nomenclature and the lack of standardised analytical methods to characterise the dietary intervention make a comparison of studies very difficult and often impossible. This might explain the lack of reliable data on intake-response relationships in meta-analyses. The recent Cochrane review for example only investigates the effect of the intervention without taking the amount or composition into consideration (Ried et al., 2017). Other studies used different approaches to explore intake-response relationships, such as the focusing exclusively on (−)-epicatechin (Ellinger et al., 2012; Hooper et al., 2012) or using total polyphenol intake (Shrime et al., 2011). These approaches make assumptions about bioactive compounds and their mode of action for which there are currently insufficient data.

3. Outlook and conclusions

Results from smaller scale dietary intervention studies suggest that flavan-3-ol intake has a beneficial effect on cardio-vascular disease risk. Indeed, these compounds have been considered as a possible candidate for DRI-like status due to their proposed beneficial effect on cardiovascular health (Williamson and Holst, 2008; Schroeter et al., 2010; Lupton et al., 2014; Yetley et al., 2017). However, the data supporting these beneficial effects were derived

Table 2
Prospective epidemiological studies investigating associations between flavan-3-ol intake and cardiovascular disease risk. Data shown are HR (95% CI) comparing bottom *vs* top intake of flavan-3-ols.

Study	Population	Dietary assesment method	Endpoint	Results (HR, 95% CI)	
Mortality					
Zutphen Elderly	806 men	Diet history	IHD	0.49 (0.27; 0.88)	Arts et al. (2001)
			Stroke	0.81 (0.36; 1.83)	
IWHS[a]	34,489 women	FFQ	All-cause	0.98 (0.91; 1.06)	Mink et al. (2007)
			Stroke	0.95 (0.71; 1.28)	
			CHD	1.02 (0.86; 1.21)	
			CVD	0.95 (0.83; 1.09)	
Kuopio Study[a]	2 682 men	Food diary	Ischaemic stroke	0.59 (0.30; 1.14)	Mursu et al. (2008)
			CVD	1.06 (0.64; 1.65)	
CPS II	38,180 men	FFQ	CVD	0.87 (0.74; 1.04)	McCullough et al. (2012)
	60,289 women		CVD	0.79 (0.66; 0.94)	
EPIC Norfolk[a]	11,252 men	Food diary	All-cause	0.99 (0.86; 1.14)	Vogiatzoglou et al. (2015a)
			CVD	0.95 (0.74; 1.20)	
	13,633 women		All-cause	0.92 (0.78; 1.09)	
			CVD	0.81 (0.60; 1.09)	
Incidence (nonfatal and fatal)					
Zutphen Elderly	806 men	Diet history	Stroke	0.92 (0.51; 1.68)	Arts et al. (2001)
			MI	0.70 (0.39; 1.26)	
NHS	69,622 women	FFQ	Ischaemic stroke	0.87 (0.72; 1.06)	Cassidy et al. (2012)
NHS II	116,430 women	FFQ	MI	0.82 (0.61; 1.26)	Cassidy et al. (2013)
EPIC Norfolk[a]	11,252 men	Food diary	CVD	0.90 (0.81; 0.99)	Vogiatzoglou et al. (2015a)
			IHD	0.88 (0.77; 1.01)	
			Stroke	1.08 (0.82; 1.43)	
	13,633 women		CVD	1.01 (0.91; 1.13)	
			IHD	0.96 (0.80; 1.17)	
			Stroke	0.89 (0.68; 1.19)	
FHSOC	2 880	FFQ	CVD	1.00 (0.88; 1.13)[b]	Jacques et al. (2015)

[a] Indicates studies which included polymeric compounds.
[b] per 2–5 fold increase; IWHS: Iowa Women's Health Study; CPS: Cancer Prevention Study OO, NHS: Nurses Health Study; FHSOC: Framingham Heart Study Offspring Cohort.

mainly from short-term studies, which used surrogate risk markers, and often did not well-characterise the dietary interventions used. The observed health benefits therefore require confirmation at scale and greater rigor. In the context of developing dietary recommendation, it is crucial to conduct long-term intervention studies with disease endpoints and well characterised test materials. In this context of flavan-3-ol research, the currently ongoing prospective dietary intervention trial COSMOS (NCT02422745) aims at addressing several currently existing gaps. Prospective epidemiological studies can also provide additional information, in particular regarding the consumption of flavan-3-ols as part of the habitual diet. Such studies rely on the accurate assessment of dietary intake, but the currently used methods, which are almost exclusively based on self-reporting and food composition databases, are highly limited or outright unsuitable. While the limitations of self-reporting can often be overcome with more sophisticated statistical methods, such an approach may not be able to address a high variability in food content as it is not predictable. These limitations are not restricted to flavan-3-ols, but also other phenolic compounds such as anthocyanidins, flavones or flavanones where food content is also extremely variable.

Taken together, the estimated intake of flavan-3-ols based on current epidemiological studies should largely be interpreted as a marker of specific dietary patterns, but not as the actual value for a reasonably accurate intake amount. Often the results of epidemiological studies are translated into dietary recommendations either based on portion-sizes of specific foods or absolute intake amounts of any given specific compound. However, this is currently not possible for flavan-3-ols, and likely many other bioactives. Consequently, interpretations of currently available data from epidemiological studies on the dietary intake of flavan-3-ols, and other bioactives, are fraught with serious limitations, especially for establishing associations between intake and health, and thus in the context of dietary recommendations.

4. Future research priorities

For the reasons detailed above, it is important to develop alternative methods for dietary assessment. Nutritional biomarkers can provide reliable estimates of actual intake, not only for flavan-3-ols, but also of most other bioactive compounds (Jenab et al., 2009; Zamora-Ros et al., 2012; Kuhnle, 2012). Their importance has been recognised for more than two decades (Kaaks et al., 1997; Food and Nutrition Board, The National Academies of Sciences, Engineering and Medicine, 2017), but there is still a paucity of well-characterised nutritional biomarkers and there are no commonly agreed upon validation criteria. Some biomarkers have been validated using extensive and large-scale dietary intervention studies (Tasevska, 2015; Lampe et al., 2017) for individual nutrients, others have used small-scale studies to develop biomarkers for entire dietary patterns (Garcia-Perez et al., 2017), and many studies have relied on self-reported intake as reference method.

The development of nutritional biomarkers requires an accurate estimate of actual intake, which often can only be obtained from duplicate diets. Moreover, it also requires a detailed understanding of the pharmacokinetic properties of target compounds, as for example, not all flavan-3-ols are bioavailable and some are excreted via the bile and not urine. A detailed understanding of metabolism is also important as bioactives, in contrast to most micronutrients, are xenobiotics and therefore extensively metabolise. Such data are becoming more readily available, for example for (−)-epicatechin (Ottaviani et al., 2016), and development of sensitive methods and high-throughput analytical techniques has facilitated the application of a biomarker-based approach to large cohort studies.

Table 3
Dietary intervention studies investigating the effect of flavan-3-ols on systolic blood pressure.

Folin[a] mg/d	PF mg/d	(−)-Epicatechin mg/d	(+)-Catechin mg/d	PA mg/d	ΔSBP (95% CI) mmHg	Study
500	–	4	4	–	−7.1 (−11.4; −2.8)	Al-Faris (2008)
_	–	98	35	–	−5.0 (−10.8; 0.8)	Baba et al. (2007)
500	305	25	13	267	0.3 (−2.6; 3.2)	van den Bogaard et al. (2010)
755	–	–	–	–	−0.5 (−5.6; 4.6)	Crews et al. (2008)
_	902	–	–	–	−6.1 (−12.9; 0.7)	Davison et al. (2008)
_	902	–	–	–	−1.6 (−7.2; 10.4)	Davison et al. (2008)
_	372	69	28	275	−0.3 (−6.0; 5.4)	Davison et al. (2010)
_	1 052	208	58	785	−4.4 (−7.7; −1.1)	Davison et al. (2010)
_	712	138	43	530	0.9 (−2.4; 4.2)	Davison et al. (2010)
_	520	95	35	390	−5.5 (−7.1; −3.9)	Desideri et al. (2012)
_	993	185	62	746	−10.0 (−12.4; −7.6)	Desideri et al. (2012)
_	168	–	–	126	−4.0 (−7.1; −0.9)	Fraga et al. (2005)
_	213	46	–	–	1.8 (−6.8; 10.4)	Engler et al. (2004)
624	–	36	11	–	−6.9 (−14.0; 0.2)	Flammer et al. (2012)
_	–	66	22	–	−6.5 (−9.4; −3.6)	Grassi et al. (2005)
_	–	66	22	–	−11.3 (−13.3; −9.3)	Grassi et al. (2005)
1 008	–	111	36	–	−3.7 (−5.1; −2.3)	Grassi et al. (2008)
_	750	130	12	608	−5.0 (−11.3; 1.3)	Heiss et al. (2010a)
_	900	128	14	754	0.0 (−2.5; 2.5)	Heiss et al. (2015)
_	900	128	14	754	−4.0 (−8.3; 0.3)	Heiss et al. (2015)
645	414	15	153	134	1.0 (−2.5; 4.5)	Ibero-Baraibar et al. (2014)
_	495	10	46	426	3.0 (−2.0; 8.0)	Khan et al. (2012)
_	86	–	–	–	1.0 (−2.3; 4.3)	Koli (2015)
_	550	–	–	–	0.6 (−6.9; 8.1)	Shiina et al. (2009)
_	250	–	–	–	6.3 (3.3; 9.3)	Massee et al. (2015)
_	–	17	–	–	0.0 (−6.7; 6.7)	Mellor et al. (2010)
_	400	–	–	–	−0.8 (−3.2; 1.6)	Mogollon et al. (2013)
_	495	46	10	426	0.6 (−6.8; 8.0)	Monagas et al. (2009)
_	912	174	62	676	−1.0 (−4.1; 2.1)	Muniyappa et al. (2008)
325	–	–	–	–	0.0 (−6.7; 6.7)	Neufingerl et al. (2013)
_	270	–	–	–	0.7 (−1.1; 2.5)	Nickols-Richardson et al. (2014)
_	234	–	–	–	−1.0 (−8.8; 6.8)	Murphy et al. (2003)
_	805	48	21	736	3.2 (−0.2; 6.6)	Njike et al. (2011)
750	–	–	–	–	2.9 (−9.9; 15.7)	Ried et al. (2009)
_	450	–	–	–	−5.3 (−7.6; −3.1)	Rostami et al. (2015)
_	1 064	–	–	841	−1.0 (−3.3; 1.3)	Rull et al. (2015)
_	900	128	14	754	−4.0 (−6.5; −1.5)	Sansone et al. (2015)
500	–	66	22	–	−5.1 (−6.1; −4.1)	Taubert et al. (2003)
_	–	5	2	–	−3.0 (−4.0; −2.1)	Taubert et al. (2007)
_	494	89	21	384	−2.8 (−5.9; 0.3)	Tzounis et al. (2011)

[a] Polyphenol content assessed using the Folin-Ciocalteau assay (Folin et al., 1915); PF: polyphenols; PA: proanthocyanidins, degree of polymerisation up to 10.

The development, validation and application of biomarkers is crucial for elucidating associations between intake of bioactives and health outcomes. There are currently some limitations to the development and application of nutritional biomarkers, and they need to be addressed urgently. Most importantly is the development of validation criteria, for example based on those suggested by IARC (Kaaks et al., 1997), and the Institute of Medicine (Institute of Medicine (US) Committee on Qualification of Biomarkers and Surrogate Endpoints in Chronic Disease et al., 2010). With the increasing importance of high-quality data from epidemiological studies for the development of dietary advice for the prevention and maintenance of chronic diseases, the development of such criteria is crucial.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.mam.2017.10.003.

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